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10/597,054	07/02/2007	Julian P. Whitelegge	67789-096US0	5324

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DAVIS WRIGHT TREMAINE LLP/Los Angeles
865 FIGUEROA STREET
SUITE 2400
LOS ANGELES, CA 90017-2566

EXAMINER

RIDER, LANCE W

ART UNIT	PAPER NUMBER
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1618

NOTIFICATION DATE	DELIVERY MODE
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06/01/2010

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentlax@dwt.com
sethlevy@dwt.com

Office Action Summary	Application No. 10/597,054	Applicant(s) WHITELEGGE ET AL.	
	Examiner LANCE RIDER	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

The remarks and amendments filed on March 15th 2010 are acknowledged.
Claims 1-10 and 12-23 are amended, claim 11 is canceled.

Response to arguments

Withdrawn Rejections

Receipt and consideration of Applicants' amended claim set and remarks filed on March 15th 2010 is acknowledged. Rejections and objections not reiterated from previous office actions are hereby withdrawn. The following rejections or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Maintained Rejections

Applicant's arguments, starting on page 8, of the reply filed on March 15th, 2010 with respect to the following rejections under 35 USC 112 1st, 112 2nd, and 102(b) have been fully considered but are not found persuasive:

Claim Rejections - 35 USC § 112 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 19-23 under 35 U.S.C. 112 first paragraph, for failing to comply with the written description requirement are maintained.

Applicant argues that the specification meets the written description requirement, and one of skill in the art at the time of the invention would recognize how to analyze subtle isotope modifications using Isosolv.

In response to applicant's argument, applicant states:

The Isosolv algorithm uses standard techniques to estimate the isotope envelope for a compound given the proportions of the different isotopes for each element in that compound. These standard techniques are known in the art; for example, Mass Spectrometry by J H Gross, pp. 74-87, or various tools available on the Internet such as, Isotope and IsoPat.

Isosolv is not claiming a method to calculate isotope distributions. Isosolv is an algorithm to estimate, from measured isotope abundances, the amount of a particular isotope in an analyte. One of skill in the art will readily know that this is performed by iteratively calculating theoretical mass spectra that would result of differing probabilities for a given isotope until a best fit mass spectrum is maintained. The probability for the isotope that yields the best fit is then returned.

First the presence of programs that perform applicant's stated goal or render obvious applicant's invention does not mean that applicant has met the written description requirement. Applicant must have described their invention in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

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invention. Applicant did not use standard equations, cite or appropriately include by reference any of the pertinent prior art, or fully describe how Isosolv functions.

Second the disclosure being relied on states that

The change in isotope distribution is readily apparent from the spectra and $^{13}\text{C}/^{12}\text{C}$ ratio was calculated from peak heights and areas using the Isosolv algorithm. **The Isosolv algorithm, explained further in example 7, measures carbon isotope distribution...**

...When given an elemental composition Isosolv uses this for estimation of $^{13}\text{C}/^{12}\text{C}$ ratio. When given a molecular weight, the number of carbons is estimated by dividing the molecular weight by 110 (the average mass of an amino acid) and multiplying by 4.94 (the average number of carbons per amino acid). Then, given a measured isotopic distribution, the ^{13}C probability can be determined by calculating the difference between the measured distribution and the theoretical distribution for an arbitrary ^{13}C abundance. The estimated ^{13}C abundance parameters are then incrementally altered until the error between the theoretical distribution and the calculated distribution has been minimized thus yielding the ^{13}C probability in the measured spectrum. The version of Isosolv used in these examples includes natural minor contributions of D, ^{15}N , $^{17/18}\text{O}$ only.

What does Isosolv calculate? The disclosure says it measures isotope distribution, yet the arguments say it doesn't. Further there is no mention of how the peak heights and areas are measured (did you integrate over the peaks?). The rest of the disclosure leads to even more questions of how this program operates. There is no mention of how one calculates the difference between the measured and theoretical distributions (is this a simple subtraction step?), there is no mention of how the parameters are incrementally altered (is this done by hand or another program or function?), there is no mention of how the error between the theoretical and calculated distributions is calculated and minimized (does the computer track the changes so it doesn't continue

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to alter the values in the wrong direction?, does it perform incrementally smaller steps to yield a more accurate minimizing of error?). In sum there is almost information on how this program actually functions, nor enough for the skilled artisan to understand without starting from scratch and designing their own program using mathematical techniques for data fitting.

The rejection of claims 19-23 under 35 U.S.C. 112 first paragraph for failing to comply with the enablement requirement are maintained.

Applicant argues that claims 19-23 comply with the enablement requirement.

In response to applicant's argument, the term "subtle" is still indefinite and the steps Isosolv performs are still unclear as stated above. The example still does not clarify how Isosolv takes into account the distribution of ^{15}N , D, and $^{17/18}\text{O}$, and there is no clear teaching of how one Isosolv functions or how one uses Isosolv. The term "subtle" is indefinite because there is no indication as to what magnitudes of changes are "subtle" and what magnitudes are "not subtle."

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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The rejection of claims 1-6, 8-10, 12-23 under 35 U.S.C. 112 second paragraph for being indefinite and failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are maintained.

Applicant argues that the skilled artisan would recognize the range that the term "subtle" defines.

In response to applicant's argument, applicant states

...As the definition provides, the minimal amount of change is that amount that produces a "measurable effect upon the observed peptide isotope distribution." One of skill in the art is able to ascertain when an isotope modification results in a measurable effect: for example, by analyzing a sample with a spectrometer. Therefore, the minimal amount of change is an amount that produces an effect on the observed peptide isotope distribution that can be measured. One of skill in the art will also know that a change that induces "a gross extension or displacement of the single isotope envelope" will not be considered subtle.

There is no actual limit upon what applicant considers a "gross extension" to be. If one examines the specification applicant claims that subtle ratios are 100:1-200:1 or 100:2 $^{13}\text{C}:^{12}\text{C}$ (99.5 to 98% ^{13}C) or 1% ^{13}C altered to 2.6%, 3.1%, and 7.1%. Even when every number or range applicant discloses is considered, a range of 1-99.5% ^{13}C is found. As there is no way for the artisan to determine what magnitudes of extension are "gross extensions" and what magnitudes are "not gross extensions" this claim still remains indefinite even in light of applicant's arguments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 6, 8-10, 12, 15, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Ong, S., et al., (Molecular and Cellular Proteomics, 2002)

Claims 1-3, 6, 8-12, 15, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Pasa-Tolie, et al., (JACS, 1999).

Claims 1-3, 6, 8-12, 15, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Oda, Y., et al., (PNAS, 1999).

Applicant argues the following:

1) Ong does not teach subtle isotope modification but rather full isotope exchange.

2) Pasa-Tolie does not teach subtle isotope modification but rather a 100% change in the ^{13}C in the sample.

3) Oda does not teach subtle isotope exchange but rather a greater than 96% replacement with ^{15}N .

In response to applicant's arguments 1-3, Ong, Pasa-Tolie, and Oda all teach proteomic expression analysis using isotopically substituted samples have 0, 1.1, 96, and 100% substitution. All the arguments are predicated on the idea that the prior art does not teach "subtle" modification. As "subtle" is indefinite and does not denote any particular magnitude of change, the prior art is still deemed valid.

In reference to applicant's remarks regarding Pasa-Tolie, Pasa-Tolie teaches using samples with 0% substitution and 1.1% ^{13}C . Applicant interpreted this to be a 100% change in the isotopic ratio, and stated that this was not a "subtle" change. In the specification however, applicant only has ranges from about 0.5-1% $^{13}\text{C}:^{12}\text{C}$ and examples with 1% ^{13}C altered to 2.6%, 3.1%, and 7.1%, all of which overlap or are beyond this level of substitution. This raises the question: did applicant perform any "subtle" modifications themselves?

These rejections are MAINTAINED for the reasons of record set forth in the Office Action mailed on October 15th 2009 and for the reasons set forth below.

New Grounds of Rejection

Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The amendment filed March 15th 2010 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The newly added formula " $\text{prob}(n) = \text{combin}(x,n) * P^n * (1-P)^{(X-n)}$ ". The function previously claimed had no superscript in the claim and this is not an insignificant change which one would

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immediately suspect. One would not know which parts were superscript and which were not and one would reasonably suspect applicant had correctly written a formula which is used to limit their claims.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims contain the term Isosolv which relies upon a newly added probability distribution function which was not included in the original specification. The function previously claimed had no superscript in the claim and this is not an insignificant change which one would immediately suspect. One would not know which parts were superscript and which were not and one would reasonably suspect applicant had correctly written a formula which is used to limit their claims. The claims also contain the range of "¹²C:¹³C of about 100:1 to about 100:2". The range claimed was also not present in applicant's specification, only a range of ¹³C:¹²C of

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about 100:1 to about 100:2 or 200:1 were present indicating a range of 98-99.5 ^{13}C , not the presently claimed 0.5-2% ^{13}C .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Hansen, K.C., et al., Molecular and Cellular Proteomics, 2003).

Hansen teaches methods of performing expression proteomic analyzing using a ^{13}C ligand with 9 labeled carbons that is used to label cysteine residues in proteins. The labeled and unlabeled proteins are measured using MSMS. The method is used to monitor the turnover of proteins in human tracheal gland secretions, meeting the limitations of instant claims 1-6, 8-10, 12-15, and 17-18. (See page 309, paragraph 2.)

The method is stated to be applicable to all protein samples, thus labeling a protein having ~450-900 carbon atoms that contains only one cysteine residue would inherently meet the limitations of claims 7 and 16 as the ligand only labels at cysteine residues. Labeling 1 residue in the protein would lead to an isotopic ratio of from about 100:1 to about 100:2 $^{12}\text{C}:^{13}\text{C}$ with 9 ^{13}C carbons being labeled and the rest being unlabeled.

Hansen tests mixed samples of hundred of different proteins, However Hansen does not identify a specific protein in the samples which has 1 cysteine and has 400-900 carbons.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to label any protein of interest (including those in containing only 1 cysteine and having 400-900 carbon atoms) with the ICAT reagent in order to perform proteomic expression analysis on that proteins. One of ordinary skill in the art at the

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time of the invention would have been motivate to perform this method in order to analyze the expression of a protein of interest. One would have predicted that this method would function as there is no modification of the method, it only depends upon what protein sample is being used, and all of the method steps remain the same.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art
Unit 1618